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Abstract

Objective To investigate the efficacy and safety of ocrelizumab in patients with class III/IV lupus nephritis (LN). Methods Patients were randomized 1:1:1 to receive placebo, 400 mg ocrelizumab, or 1,000 mg ocrelizumab given as an intravenous infusion on days 1 and 15, followed by a single infusion at week 16 and every 16 weeks thereafter, accompanied by background glucocorticoids plus either mycophenolate mofetil (MMF) or the Euro-Lupus Nephritis Trial (ELNT) regimen (cyclophosphamide followed by azathioprine). The study was terminated early due to an imbalance in serious infections in ocrelizumab-treated patients versus placebo-treated patients. We report week 48 efficacy data for patients receiving ≥32 weeks of treatment (n = 223) and safety results for all treated patients (n = 378). Results The overall renal response rate was 54.7%, 66.7%, 67.1%, and 66.9% in the placebo-treated, 400 mg ocrelizumab-treated, 1,000 mg ocrelizumab-treated, and combined ocrelizumab-treated groups,...

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Efficacy and Safety of Ocrelizumab in Active Proliferative Lupus Nephritis

Results From a Randomized, Double-Blind, Phase III Study

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Results. **The overall renal response rate was 54.7%, 66.7%, 67.1%, and 66.9% in the placebo-treated, 400 mg ocrelizumab–treated, 1,000 mg ocrelizumab–treated, and combined ocrelizumab-treated groups, respectively. The associated treatment difference versus placebo for the combined ocrelizumab-treated groups was 12.7% (95% confidence interval [95% CI] −0.8, 26.1) ($P = 0.065$), with similar differences observed for both ocrelizumab-treated groups. Ocrelizumab versus placebo treatment differences were apparent in patients receiving the background ELNT regimen, but not in those receiving background MMF. A numerically greater proportion of ocrelizumab-treated patients had a ≥50% reduction in the urinary protein:urinary creatinine ratio at 48 weeks compared with placebo-treated patients (placebo-treated patients, 58.7%; 400 mg ocrelizumab–treated patients, 70.7%; 1,000 mg ocrelizumab–treated patients, 68.5%). Serious adverse events occurred in 27.2% of placebo-treated patients, 35.7% of 400 mg ocrelizumab–treated patients, and 22.0% of 1,000 mg ocrelizumab–treated patients. Corresponding serious infection rates (events/100 patient-years) were 18.7 (95% CI 12.2, 28.7), 28.8 (95% CI 20.6, 40.3), and 25.1 (95% CI 17.4, 36.1), respectively. The imbalance in serious infections with ocrelizumab oc-**

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curred with background MMF but not with the background ELNT regimen.

***Conclusion*. In patients with active LN, overall renal response rates with ocrelizumab were numerically but not statistically significantly superior to those with placebo. Ocrelizumab treatment was associated with a higher rate of serious infections in the subgroup receiving background MMF.**

Approximately 60% of patients with systemic lupus erythematosus (SLE) develop renal involvement (lupus nephritis [LN]), and LN remains an important contributor to the increased morbidity and mortality associated with SLE (1). The standard treatment for LN is guided by histologic classification according to International Society of Nephrology/Renal Pathology Society criteria (2), with treatment of patients with class III/IV LN usually involving a short period of intense induction therapy followed by a prolonged period of maintenance treatment (3). Based on the results of several robust clinical trials (4–10), recent guidelines published by the American College of Rheumatology (ACR) (11) and the European League Against Rheumatism/European Renal Association–European Dialysis and Transplant Association (12) recommend mycophenolate mofetil (MMF) or cyclophosphamide (CYC) for induction of improvement in patients with International Society of Nephrology class III/IV lupus glomerulonephritis (11).

B cells are strongly implicated in the pathogenesis of SLE and LN (13–17). Belimumab, a monoclonal antibody that neutralizes the B cell survival factor B lymphocyte stimulator, recently received Food and Drug Administration approval for the treatment of SLE (18). In addition, rituximab, a chimeric anti-CD20 monoclonal antibody, has shown encouraging results in several studies (19–21). Recently, rituximab was evaluated in a large, international, randomized, placebo-controlled trial (Lupus Nephritis Assessment of Rituximab [LUNAR]) in patients with class III or class IV LN (22). In the LUNAR trial, there were numerically more responders in the rituximab-treated group, but the 11% difference versus placebo was not statistically significant (patients with complete or partial renal response at week 52: rituximab-treated 56.9%, placebo-treated 45.8%; $P = 0.18$).

Ocrelizumab (2H7) is a recombinant humanized monoclonal antibody that also selectively targets and depletes CD20+ B cells in the peripheral circulation. Ocrelizumab possesses enhanced antibody-dependent cell-mediated cytotoxicity and reduced complement-dependent cytotoxicity compared with rituximab in vitro (data on file; Genentech) and was originally investigated in a phase II study in patients with rheumatoid arthritis (RA) (23). A comprehensive phase III program further evaluated ocrelizumab in RA. Two pivotal trials tested ocrelizumab at 2 dose levels (2×200 mg and 2×500 mg, with the doses given 2 weeks apart) in combination with methotrexate (MTX) (24,25). Both doses improved the signs and symptoms of RA and also significantly reduced progressive joint damage in the STAGE study, a randomized, double-blind, parallel-group international study to evaluate the safety and efficacy of ocrelizumab compared with placebo in patients with active RA continuing MTX treatment (25). Although the overall incidence of adverse events (AEs) and infections was similar between ocrelizumab and placebo in both trials, a higher rate of serious infections was observed with the higher dose compared with placebo in the STAGE study (25) and with both doses in the SCRIPT study, a randomized, double-blind, parallel-group international study to evaluate the safety and efficacy of ocrelizumab compared with placebo in patients with active RA who have had an inadequate response to at least 1 anti–tumor necrosis factor therapy (24).

The current, BELONG study, a study to evaluate ocrelizumab in patients with nephritis due to SLE, was conducted to determine the efficacy and safety of ocrelizumab compared with placebo in patients with active LN who were also receiving glucocorticoids plus standard of care of CYC (Euro-Lupus Nephritis Trial [ELNT] regimen) or MMF. An imbalance in the rate of serious and opportunistic infections in ocrelizumab-treated patients, together with the results from the rituximab LUNAR study (22), led the sponsor to reassess the benefit/risk ratio of anti-CD20 therapy in patients with LN and to terminate the BELONG study early. As a result, this report includes safety data for all treated patients and week 48 efficacy data for patients who had received treatment within the study for at least 32 weeks.

PATIENTS AND METHODS

Patients. Patients were age ≥16 years and had SLE according to the ACR 1982 revised criteria (26), including a history of antinuclear antibody positivity and active LN (defined as a urinary protein:urinary creatinine ratio ≥1 with biopsy-proven [within 6 months prior to randomization] World Health Organization [WHO] [2] or International Society of Nephrology class III or IV LN [excluding III (C), IV-S (C), and IV-G (C)], with coexisting class V permitted; or WHO class III or IV glomerulonephritis, provided that ≤50% of glomeruli showed sclerosis or fibrosis). Key exclusion criteria were active

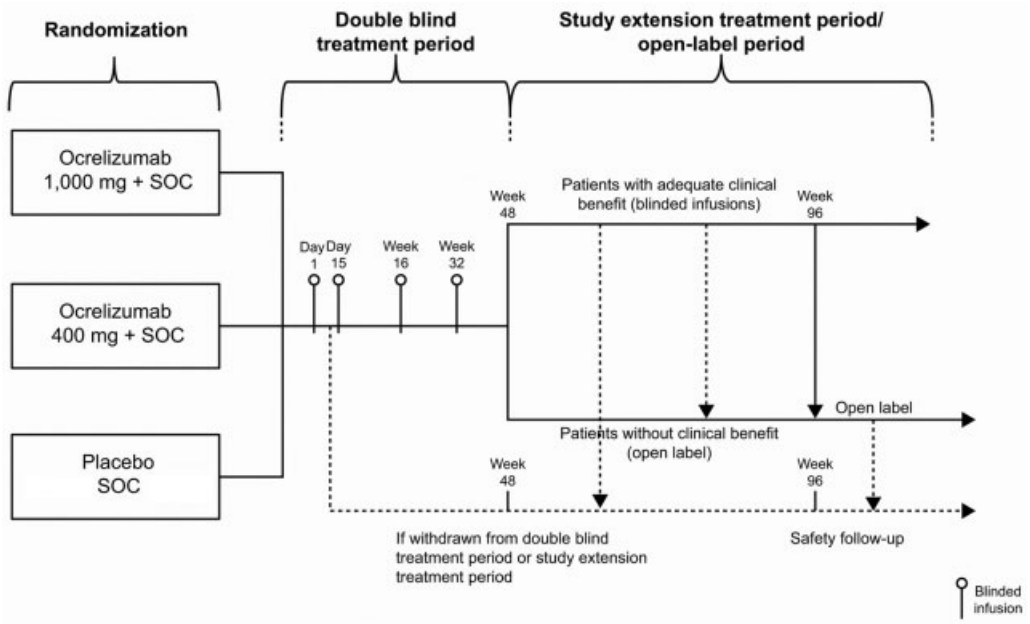

Figure 1. Study design. SOC = standard of care.

retinitis, poorly controlled seizure disorder, acute confusional state, myelitis, stroke or stroke syndrome, cerebellar ataxia or dementia, severe renal impairment, estimated glomerular filtration rate <25 ml/minute per 1.73 m^2 of body surface area, end-stage renal disease requiring dialysis or transplant, thrombocytopenia, or experiencing or at high risk of developing clinically significant bleeding or organ dysfunction.

Study design. This was a multicenter, randomized, double-blind, placebo-controlled, parallel-group, phase III study (Figure 1). The initial double-blind, placebo-controlled period lasted 48 weeks. Patients with an adequate clinical response at 48 weeks continued blinded treatment through week 96, while those with an inadequate clinical response could receive open-label treatment. Safety followup started when a patient discontinued from any of the treatment periods for any reason, and patients remained in safety followup for at least 48 weeks following the last infusion of study drug.

Patients were randomized 1:1:1 to receive placebo, 400 mg ocrelizumab, or 1,000 mg ocrelizumab given as an intravenous (IV) infusion on days 1 and 15, followed by a single infusion at week 16 and every 16 weeks thereafter. All patients received MMF (target dose 3 gm/day) or CYC (ELNT regimen: 500 mg IV every 2 weeks × 6). The choice of background induction therapy regimen was at the discretion of the investigator. Patients receiving MMF continued to receive MMF, while patients receiving the ELNT CYC regimen were subsequently treated with azathioprine (AZA; 2 mg/kg up to 200 mg/day, dose selected by the investigator). IV steroids (up to 3 gm/day) were also permitted by day 15, given in divided pulses, and oral steroids (0.5–0.75 mg/kg [≤60 mg/day]) were allowed with taper to ≤10 mg over 10 weeks. Before each infusion, patients were administered IV methylprednisolone (100 mg), acetaminophen/paracetamol (1 gm), and an antihistamine (50 mg IV diphenhydramine HCl or equivalent). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki or with the laws and regulations of the country in which the research was conducted, and all patients provided written informed consent.

Efficacy assessments. Clinical response was assessed in the following 3 mutually exclusive categories at week 48: complete renal response (normal serum creatinine [≤25% increase from baseline] and improvement in urinary protein: urinary creatinine ratio to <0.5), partial renal response (serum creatinine ≤25% above baseline, and 50% improvement in urinary protein:urinary creatinine ratio, and if baseline ratio >3.0, then urinary protein:urinary creatinine ratio <3.0), and nonresponse (no complete or partial renal response). Death or discontinuation from the study prior to week 48 (and no renal data available within 12 weeks of week 48) was considered a nonresponse.

Safety assessments. AEs were recorded throughout the study and graded according to the National Cancer Institute Common Terminology Criteria for Adverse Events, version 3.

Statistical analysis. Based on an estimated complete renal response rate of 40% in the ocrelizumab-treated group and 30% in the placebo-treated group, a partial renal response rate of 40% in the ocrelizumab-treated group and 25% in the placebo-treated group, and a nonresponse rate of 20% in the ocrelizumab-treated group and 45% in the placebo-treated group, and allowing for a 15% dropout rate, 369 patients (123 per treatment arm) were required to detect a difference with 80% power between active and control treatment arms at a 2-sided alpha level of 0.025.

The analysis population for efficacy outcomes consisted of a subset of randomized patients treated for ≥32 weeks prior to study termination, and who had a baseline urinary protein:urinary creatinine ratio ≥1 (a few treated

Table 1. Reasons for withdrawal from treatment prior to week 48*

Reason	Placebo (n = 125)	Ocrelizumab 400 mg (n = 126)	Ocrelizumab 1,000 mg (n = 127)
Discontinued prior to week 48	80 (64.0)	79 (62.7)	80 (63.0)
Adverse event/intercurrent illness	3 (2.4)	6 (4.8)	3 (2.4)
Death	3 (2.4)	0	4 (3.1)
Insufficient therapeutic response	1 (0.8)	2 (1.6)	0
Failure to return	0	1 (0.8)	1 (0.8)
Violation of selection criteria at entry	1 (0.8)	0	1 (0.8)
Other protocol violation	1 (0.8)	0	2 (1.6)
Refused treatment/did not cooperate	0	1 (0.8)	1 (0.8)
Withdrew consent	3 (2.4)	4 (3.2)	1 (0.8)
Administrative/other†	68 (54.4)	65 (51.6)	67 (52.8)

* Values are the number (%) of patients.
† The vast majority of withdrawals in this category were due to the early termination of the study.

patients did not meet this entry criterion). This population (modified intent-to-treat [ITT] population) was defined after the decision to stop dosing. The cutoff of 32 weeks was used because it included patients who had the opportunity to receive at least 4 double-blind infusions of study drug with outcomes least biased by the decision to stop the study.

The primary end point was the proportion of patients with a renal response (complete renal response, partial renal response, or nonresponse) at week 48. Renal responses in the 3 categories were summarized descriptively; the difference in overall renal response (complete renal response or partial renal response) at week 48 was analyzed using the Cochran-Mantel-Haenszel test, adjusting for race and standard of care.

The safety population comprised all patients who received at least 1 infusion of ocrelizumab or placebo. Safety data up to week 48 are presented descriptively.

RESULTS

Patient population. At the time of study termination (October 19, 2009), 381 patients from 123 sites in 23 countries had been randomized to study treatment (the ITT population). Three patients who were randomized (1 from each study group) did not receive treatment, 1 due to an AE, 1 for administrative reasons, and 1 due to withdrawal of consent. The remaining 378 patients received at least 1 infusion of ocrelizumab or placebo (the safety population). Due to the early study termination, only 139 patients (36.8%) completed the 48-week, double-blind treatment period. The reasons for withdrawal are shown in Table 1. The modified ITT population for efficacy analysis consisted of 223 patients (75, 75, and 73 patients in the placebo-treated, 400 mg ocrelizumab–treated, and 1,000 mg ocrelizumab–treated groups, respectively).

This was the first trial outside Europe to enroll patients in an ELNT regimen. Patients were included from sites in Latin America (42%), Asia (23.1%), Western Europe (12.9%), Eastern Europe (10.5%), the US and Canada (10.2%), and Africa (1.3%). Overall, 63% of patients received MMF and 37% received the ELNT regimen. Use of the ELNT regimen ranged from 68% in Eastern Europe to 18% in the US and Canada. Patients reached the target MMF dose of 3 gm/day in 3 weeks, and MMF was not tapered before week 48.

Baseline demographic characteristics were well balanced, although the 1,000 mg ocrelizumab–treated group had a slightly higher proportion of white patients and a lower proportion of Asian patients than did the other 2 groups (Table 2). In general, there were no notable differences between the groups in the frequency of concomitant medication use during the treatment period, except for a somewhat lower proportion of patients in the 1,000 mg ocrelizumab–treated group who used statins and angiotensin II receptor antagonists (data not shown). All patients received IV glucocorticoids at baseline (during screening or on day 1). The cumulative IV glucocorticoid dose received during screening/day 1 was similar between treatment groups (overall median dose 500 mg [range 100–3,100 mg]). However, the IV glucocorticoid dose received on day 1 was lower for patients receiving the ELNT regimen than for patients receiving MMF (median 100 mg versus 500 mg).

Efficacy. The overall renal response rate at 48 weeks was 54.7%, 66.7%, and 67.1% in the placebo-treated, 400 mg ocrelizumab–treated, and 1,000 mg ocrelizumab–treated groups, respectively (Table 3). The overall renal response rate for the 2 ocrelizumab-treated groups combined was 66.9%. The associated treatment differences (versus placebo) were 12.1% (95% confi-

Table 2. Baseline demographics and disease characteristics of the randomized patients*

Characteristic	Placebo (n = 126)	Ocrelizumab 400 mg (n = 127)	Ocrelizumab 1,000 mg (n = 128)	Total (n = 381)
Female, no. (%)	107 (84.9)	115 (90.6)	110 (85.9)	332 (87.1)
Age				
Mean (range) years	31.3 (17–66)	31.9 (16–69)	30.6 (16–60)	31.3 (16–69)
<30 years, %	51	47	53	50
Race, no. (%)				
White	58 (46.0)	55 (43.3)	67 (52.3)	180 (47.2)
Asian	35 (27.8)	39 (30.7)	27 (21.1)	101 (26.5)
American Indian/Native Alaskan	17 (13.5)	17 (13.4)	15 (11.7)	49 (12.9)
Black	5 (4.0)	7 (5.5)	7 (5.5)	19 (5.0)
Other	11 (8.7)	9 (7.1)	12 (9.4)	32 (8.4)
Ethnicity, no. (%)				
Hispanic	51 (40.5)	58 (45.7)	58 (45.3)	167 (43.8)
Non-Hispanic	75 (59.5)	69 (54.3)	70 (54.7)	214 (56.2)
LN class, no. (%)				
III	30 (23.8)	23 (18.1)	25 (19.5)	78 (20.5)
IV	96 (76.2)	104 (81.9)	103 (80.5)	303 (79.5)
V with III/IV	23 (18.3)	21 (16.5)	25 (19.5)	69 (18.1)
Time from biopsy to randomization, median (range) days	32 (4–168)	27.5 (2–134)	32 (5–195)	31 (2–195)
SLE duration, median (range) years	3.9 (0–20)	3.9 (0–20)	3.9 (0–25)	3.9 (0–25)
LN duration, median (range) years	0.6 (0–19)	0.8 (0–20)	0.7 (0–20)	0.7 (0–20)
Patients receiving background MMF	0.9 (0–19)	1.5 (0–16)	1.2 (0–20)	1.1 (0–20)
Patients receiving background ELNT regimen	0.3 (0–15)	0.4 (0–20)	0.4 (0–19)	0.3 (0–20)
Asian patients	4.4 (0–14)	1.4 (0–11)	3.2 (0–20)	2.1 (0–20)
Non-Asian patients	0.4 (0–19)	0.8 (0–19)	0.6 (0–18)	0.6 (0–19)
Urinary protein:urinary creatinine ratio (24 hours), median (% with median >3)	2.7 (46)	3.0 (50)	2.9 (50)	2.8 (49)
Patients receiving background MMF	2.5 (45)	2.6 (46)	2.8 (46)	2.6 (46)
Patients receiving background ELNT regimen	2.9 (48)	3.6 (58)	4.1 (56)	3.3 (54)
Asian patients	2.9 (50)	3.8 (66)	3.6 (57)	3.5 (58)
Non-Asian patients	2.6 (45)	2.5 (45)	2.8 (49)	2.6 (46)
Serum creatinine, mean ± SD mg/dl				
Patients receiving background MMF	0.9 ± 0.4	1.0 ± 0.6	1.0 ± 0.5	0.9 ± 0.5
Patients receiving background ELNT regimen	0.9 ± 0.4	1.1 ± 0.8	1.0 ± 0.5	1.0 ± 0.6
Asian patients	0.8 ± 0.4	1.0 ± 0.5	1.0 ± 0.5	0.9 ± 0.5
Non-Asian patients	0.9 ± 0.4	1.0 ± 0.7	1.0 ± 0.5	1.0 ± 0.6
C3, mean ± SD mg/dl	65 ± 26	71 ± 47	69 ± 31	68 ± 36
C4, mean ± SD mg/dl	15 ± 9	15 ± 7	15 ± 7	15 ± 7
Anti-dsDNA, geometric mean IU/ml	121	100	117	112

* LN = lupus nephritis; SLE = systemic lupus erythematosus; MMF = mycophenolate mofetil; ELNT = Euro-Lupus Nephritis Trial; anti-dsDNA = anti–double-stranded DNA.

dence interval [95% CI] −3.3, 27.5), 13.9% (95% CI −1.4, 29.2), and 12.7% (95% CI −0.8, 26.1) for the 400 mg ocrelizumab–treated, 1,000 mg ocrelizumab–treated, and the 2 ocrelizumab-treated groups combined, respectively. A numerically greater proportion of ocrelizumab-treated patients had a ≥50% reduction in the urinary protein:urinary creatinine ratio at 48 weeks compared with placebo-treated patients (placebo-treated patients, 58.7%; 400 mg ocrelizumab–treated patients, 70.7%; 1,000 mg ocrelizumab–treated patients, 68.5%). The proportion of patients with a urinary protein:urinary creatinine ratio <0.5 at 48 weeks was 37.3%, 44.0%, and 35.5% in the placebo-treated, 400 mg ocrelizumab–treated, and 1,000 mg ocrelizumab–treated groups, respectively.

Week 48 renal response by standard of care regimen. When stratified by background standard of care, there was a trend ($P = 0.065$) toward greater overall renal response rates at 48 weeks with ocrelizumab treatment and the ELNT regimen versus placebo treatment and the ELNT regimen (Table 3). Adjusted treatment differences (versus placebo) were 31.3% (95% CI 7.4, 55.3) and 14.7% (95% CI –10.0, 39.6) for the 400 mg ocrelizumab–treated and 1,000 mg ocrelizumab–treated groups, respectively. Higher observed overall renal response rates and complete renal response rates in the

Table 3. Renal response rates at week 48, overall and by background standard of care (modified intent-to-treat population)*

Response	Placebo + standard of care (n = 75)	Ocrelizumab		
		400 mg + standard of care (n = 75)	1,000 mg + standard of care (n = 73)	Combined + standard of care (n = 148)
All patients				
CRR, no. (%)	26 (34.7)	32 (42.7)	23 (31.5)	55 (37.2)
PRR, no. (%)	15 (20.0)	18 (24.0)	26 (35.6)	44 (29.7)
ORR, no. (%)	41 (54.7)	50 (66.7)	49 (67.1)	99 (66.9)
95% CI for the ORR, %	43.4, 65.9	56.0, 77.3	56.3, 77.9	59.3, 74.5
Adjusted treatment difference, % (95% CI)†	–	12.1 (−3.3, 27.5)	13.9 (−1.4, 29.2)	12.7 (−0.8, 26.1)
P‡	–	–	–	0.065
ELNT regimen§				
CRR, no. (%)	7 (25)	14 (45)	8 (24)	22 (34)
PRR, no. (%)	5 (18)	9 (29)	11 (33)	20 (31)
ORR, no. (%)	12 (43)	23 (74)	19 (58)	42 (66)
95% CI for the ORR, %	24.5, 61.2	58.8, 89.6	40.7, 74.4	54.0, 77.3
Adjusted treatment difference, % (95% CI)†	–	31.3 (7.4, 55.3)	14.7 (−10.0, 39.6)	22.8 (1.1, 44.5)
P‡	–	–	–	0.065
MMF§				
CRR, no. (%)	19 (40)	18 (41)	15 (38)	33 (39)
PRR, no. (%)	10 (21)	9 (20)	15 (38)	24 (29)
ORR, no. (%)	29 (62)	27 (61)	30 (75)	57 (68)
95% CI for the ORR, %	47.8, 75.6	47.0, 75.8	61.6, 88.4	57.9, 77.8
Adjusted treatment difference, % (95% CI)†	–	−0.3 (−20.0, 19.7)	13.3 (−6.0, 32.6)	6.2 (−11, 23.3)
P‡	–	–	–	0.57

* CRR = complete renal response; PRR = partial renal response; ORR = overall renal response (complete renal response combined with partial renal response); 95% CI = 95% confidence interval (see Table 2 for other definitions).
† Stratified by standard of care regimen and compared with placebo.
‡ Versus placebo, by Cochran-Mantel-Haenszel test.
§ Among patients receiving the background ELNT regimen, 28 were receiving placebo, 31 were receiving 400 mg ocrelizumab, and 33 were receiving 1,000 mg ocrelizumab, for a total of 64 receiving ocrelizumab. Among patients receiving background MMF, 47 were receiving placebo, 44 were receiving 400 mg ocrelizumab, and 40 were receiving 1,000 mg ocrelizumab, for a total of 84 receiving ocrelizumab.

400 mg ocrelizumab–treated group with the ELNT regimen were consistent over time (see Supplementary Figure 1, available on the *Arthritis & Rheumatism* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.38037/abstract). Most patients receiving the ELNT regimen (82%) in the modified ITT population received at least 6 doses of 500 mg IV CYC up to week 16, with a similar frequency in all treatment groups.

Adding ocrelizumab to background MMF had little effect on the overall renal response rate, with adjusted treatment differences (versus MMF alone) of −0.3% (95% CI −20.0, 19.7) and 13.3% (95% CI −6.0, 32.6) for the 400 mg ocrelizumab–treated and 1,000 mg ocrelizumab–treated groups, respectively (Table 3). In the modified ITT population, the daily dose of MMF over the 48 weeks of treatment was comparable among the treatment groups, with mean ± SD doses of 2.2 ± 0.6, 2.0 ± 0.6, and 2.1 ± 0.7 gm/day for the placebo-treated, 400 mg ocrelizumab–treated, and 1,000 mg ocrelizumab–treated groups, respectively.

There were no apparent meaningful differences between treatment groups with respect to mean daily oral prednisone dose over the 48-week study period, both overall and within each standard of care subgroup. The mean ± SD daily dose in the modified ITT population over 48 weeks was 14 ± 6 mg (median 12 mg). After week 12, the mean and median prednisone dose was 10 mg.

In the modified ITT population, approximately one-third of patients received a baseline IV glucocorticoid dose of <500 mg, one-third received 500–<1,000 mg, and the remaining one-third received ≥1,000 mg. The proportion of patients receiving baseline IV glucocorticoid doses ≥1,000 mg was higher in the MMF group (46%, versus 22% for the ELNT regimen), with a greater difference among placebo-treated patients

Table 4. Serologic end points (modified intent-to-treat population)*

End point	Placebo + standard of care (n = 75)	Ocrelizumab		
		400 mg + standard of care (n = 75)	1,000 mg + standard of care (n = 73)	Combined + standard of care (n = 148)
Percentage of baseline at week 48 in anti-dsDNA, geometric mean (95% CI)				
All patients	54 (43, 67)	30 (24, 37)	32 (26, 39)	31 (27, 36)
Patients receiving background ELNT regimen	64 (42, 96)	34 (23, 48)	33 (23, 48)	33 (26, 43)
Patients receiving background MMF	49 (38, 64)	28 (21, 36)	31 (24, 39)	29 (25, 35)
P†	–	–	–	<0.001
Patients with normalized anti-dsDNA levels at week 48, % (no./total no.)				
All patients	14 (8/57)	31 (18/58)	25 (15/60)	28 (33/118)
Patients receiving background ELNT regimen	14 (3/22)	30 (7/23)	35 (9/26)	33 (16/49)
Patients receiving background MMF	14 (5/35)	31 (11/35)	18 (6/34)	25 (17/69)
P‡	–	–	–	0.044
Change from baseline to week 48 in C3, mean + SEM mg/dl				
All patients	14.5 ± 2.6	24.1 ± 6.3	28.8 ± 3.2	26.4 ± 3.6
Patients receiving background ELNT regimen	9.5 ± 4.2	26.5 ± 6.2	29.7 ± 4.7	28.1 ± 30.5
Patients receiving background MMF	17.5 ± 3.3	22.4 ± 9.9	28.2 ± 4.5	25.1 ± 51.6
P†	–	–	–	<0.001
Patients with normalized C3 levels at week 48, % (no./total no.)				
All patients	22 (14/65)	55 (34/62)	63 (36/57)	59 (70/119)
Patients receiving background ELNT regimen	21 (5/24)	52 (13/25)	74 (17/23)	63 (30/48)
Patients receiving background MMF	22 (9/41)	57 (21/37)	56 (19/34)	56 (40/71)
P‡	–	–	–	<0.001
Change from baseline to week 48 in C4, mean + SEM mg/dl				
All patients	1.3 ± 0.8	4.9 ± 0.9	5.2 ± 0.8	5.1 ± 0.6
Patients receiving background ELNT regimen	−0.5 ± 1.9	5.4 ± 1.8	5.0 ± 1.1	5.2 ± 1.0
Patients receiving background MMF	2.3 ± 0.6	5.0 ± 1.1	5.4 ± 1.1	5.0 ± 0.7
P†	–	–	–	<0.001
Patients with normalized C4 levels at week 48, % (no./total no.)				
All patients	25 (14/56)	54 (26/48)	54 (26/48)	54 (52/96)
Patients receiving background ELNT regimen	20 (4/20)	59 (13/22)	56 (10/18)	58 (23/40)
Patients receiving background MMF	28 (10/36)	50 (13/26)	53 (16/30)	52 (29/56)
P‡	–	–	–	<0.001

* 95% CI = 95% confidence interval (see Table 2 for other definitions).
† Versus placebo, by analysis of covariance with adjustment by standard of care and baseline value.
‡ Versus placebo, by Cochran-Mantel-Haenszel test with stratification by standard of care for patients with abnormal levels at baseline.

(51% versus 11%). An exploratory ad hoc analysis showed that patients who received higher baseline IV glucocorticoid doses had higher overall renal response rates, particularly placebo-treated patients (38%, 50%, and 74% for patients receiving glucocorticoid doses of <500 mg, 500 to <1,000 mg, and ≥1,000 mg, respectively). In addition, a difference in overall renal response rates between placebo and ocrelizumab was only observed in the 2 subgroups with lower baseline IV glucocorticoid doses; overall renal response rates were similar between placebo and ocrelizumab (74% and 72%, respectively) for patients who received IV glucocorticoid doses ≥1,000 mg at baseline (see Supplementary Table 1, available on the *Arthritis & Rheumatism* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.38037/abstract). Additional exploratory subgroup analyses of overall renal response by race and by prior immunosuppressant use are presented in Supplementary Table 1.

Serologic end points. Exploratory analyses were performed on changes from baseline to week 48 in serum C3, C4, and anti–double-stranded DNA (anti-dsDNA) levels. In the modified ITT population, ocrelizumab significantly increased complement levels and significantly reduced anti-dsDNA levels at week 48 ($P < 0.001$), with similar degrees of improvement for both doses (Table 4). Among patients with abnormal levels at

Table 5. Summary of safety results over 48 weeks (safety population)*

	Placebo (n = 125)	Ocrelizumab 400 mg (n = 126)	Ocrelizumab 1,000 mg (n = 127)	All patients (n = 378)
Patients with ≥1 AE, no. (%)	110 (88.0)	109 (86.5)	102 (80.3)	321 (84.9)
Patients receiving background ELNT regimen, no./total no. (%)	36/45 (80.0)	36/47 (76.6)	29/48 (60.4)	101/140 (72.1)
Patients receiving background MMF, no./total no. (%)	74/80 (92.5)	73/79 (92.4)	73/79 (92.4)	220/238 (92.4)
Patients with serious AEs, no. (%)	34 (27.2)	45 (35.7)	28 (22.0)	107 (28.3)
Patients receiving background ELNT regimen, no./total no. (%)	17/45 (37.8)	13/47 (27.7)	9/48 (18.8)	39/140 (27.9)
Patients receiving background MMF, no./total no. (%)	17/80 (21.3)	32/79 (40.5)	19/79 (24.1)	68/238 (28.6)
Patients with infections, no. (%)	70 (56.0)	86 (68.3)	75 (59.1)	231 (61.1)
Patients receiving background ELNT regimen, no./total no. (%)	20/45 (44.4)	29/47 (61.7)	19/48 (39.6)	68/140 (48.6)
Patients receiving background MMF, no./total no. (%)	50/80 (62.5)	57/79 (72.2)	56/79 (70.9)	163/238 (68.5)
Patients with serious infections, no. (%)	18 (14.4)	27 (21.4)	19 (15.0)	64 (16.9)
Patients receiving background ELNT regimen, no./total no. (%)	5/45 (11.1)	5/47 (10.6)	5/48 (10.4)	15/140 (10.7)
Patients receiving background MMF, no./total no. (%)	13/80 (16.3)	22/79 (27.8)	15/79 (19.0)	53/238 (22.3)
Patients with opportunistic infections, no. (%)	1 (0.8)	4 (3.2)	1 (0.8)	6 (1.6)
Patients receiving background ELNT regimen, no./total no. (%)†	0	1/47 (2.1)	0	1/140 (0.7)
Patients receiving background MMF, no./total no. (%)‡	1/80 (1.3)	3/79 (3.8)	1/79 (1.3)	5/238 (2.1)
Patients with infusion-related reactions, no. (%)	11 (8.8)	15 (11.9)	18 (14.2)	44 (11.6)
Day 1, no. (%)	7 (5.6)	9 (7.1)	15 (11.8)	31 (8.2)
Day 15, no./total no. (%)§	3/122 (2.5)	6/123 (4.9)	2/124 (1.6)	11/369 (3.0)
Week 16, no./total no. (%)§	2/95 (2.1)	1/98 (1.0)	2/94 (2.1)	5/287 (1.7)
Week 32, no./total no. (%)§	0/65	1/67 (1.5)	0/65	1/197 (0.5)
Patients with serious infusion-related reactions, no. (%)	0	1 (0.8)	1 (0.8)	2 (0.5)

* AE = adverse event (see Table 2 for other definitions).
† Includes 1 case of *Pneumocystis jiroveci* and cytomegalovirus pneumonia.
‡ Includes tuberculosis (placebo), disseminated herpes zoster, systemic herpes, and cryptococcal meningitis (all 400 mg ocrelizumab), and disseminated herpes/*P jiroveci* (1,000 mg ocrelizumab).
§ The denominators are the number of patients who received the study drug at the visit.

baseline, ocrelizumab increased the proportion of patients with normalized C3, C4, and anti-dsDNA levels at week 48 ($P < 0.001$, $P < 0.001$, and $P = 0.044$, respectively) (Table 4). Stratification of patients according to serologic status indicated that clinical benefit (overall renal response at week 48) from ocrelizumab was greatest among patients with low levels of C3 and C4 at baseline (adjusted treatment difference 21% [95% CI 5, 37]) (see Supplementary Table 1, available on the *Arthritis & Rheumatism* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.38037/abstract). Patients with normal levels of C3 and C4 showed no increase in overall renal response at week 48 with ocrelizumab versus placebo (58% versus 61%, respectively). Similarly, patients with normal anti-dsDNA levels at baseline did not show an increase in overall renal response at week 48 with ocrelizumab compared with placebo (50% versus 44%, respectively).

Pharmacodynamics. Treatment with ocrelizumab led to rapid depletion of CD19+ B cells, with levels remaining well below the lower limit of normal (80 cells/μl) through week 48. Patients receiving the ELNT regimen appeared to show a somewhat greater depletion and slower repletion compared with patients receiving MMF, a difference also seen in the placebo-treated group (see Supplementary Figure 2, available on the *Arthritis & Rheumatism* web site at http://onlinelibrary.wiley.com/doi/10.1002/art.38037/abstract).

Safety. Overall, 84.9% of patients reported an AE during the 48-week, double-blind period (Table 5). The most common AEs were diarrhea (19.6%), upper respiratory tract infection (14.3%), urinary tract infection (11.9%), infusion-related reactions (11.6%), and nasopharyngitis (10.8%). In general, AEs occurred with similar frequencies in each treatment group; infusion-related reactions, however, were more frequent with ocrelizumab. Infusion-related reactions were more common with the first infusion of the first course and diminished with subsequent infusions (Table 5). Two patients in the ocrelizumab-treated groups reported serious infusion-related reactions (1 angioneurotic edema, 1 hypertension and ventricular extrasystole); both resolved without sequelae.

Overall, 28.3% of patients reported a serious AE up to week 48. Serious AEs occurred in a greater proportion of 400 mg ocrelizumab–treated patients than in placebo-treated or 1,000 mg ocrelizumab–treated patients (Table 5). Neutropenia as a serious AE was only

reported with ocrelizumab treatment (1.6% of 400 mg ocrelizumab–treated patients and 2.4% of 1,000 mg ocrelizumab–treated patients). A total of 231 patients (61.1%) reported an infection during the study, with the highest incidence in the group receiving 400 mg ocrelizumab (Table 5). Infection rates were also highest with 400 mg ocrelizumab (210.7 events [95% CI 186.1, 238.5] per 100 patient-years, compared with 149.5 events [95% CI 128.6, 174.0] per 100 patient-years for placebo and 179.1 events [95% CI 156.3, 205.2] per 100 patient-years for 1,000 mg ocrelizumab). A higher incidence of infections occurred in patients from Asia (74.7%) compared with patients from the rest of the world (57.0%).

Serious infections were reported in 16.9% of patients, the most common being pneumonia, which occurred with the highest frequency with 1,000 mg ocrelizumab (5.5%, versus 2.4% and 1.6% with 400 mg ocrelizumab and placebo, respectively). Cellulitis was the most frequently reported serious infection with 400 mg ocrelizumab, while gastroenteritis was most frequently reported in the placebo-treated group. Overall serious infection rates per 100 patient-years were 18.7 (95% CI 12.2, 28.7), 28.8 (95% CI 20.6, 40.3), and 25.1 (95% CI 17.4, 36.1) in the placebo-treated, 400 mg ocrelizumab–treated, and 1,000 mg ocrelizumab–treated groups, respectively. Overall serious infection rates per 100 patient-years were 43.0 (95% CI 30.7, 60.2) for patients recruited in Asia and 18.7 (95% CI 14.2, 24.7) for those recruited outside of Asia. A similar trend was seen when each treatment group was analyzed separately.

Six opportunistic infections were reported (Table 5). All but 1 case occurred in patients receiving background MMF therapy, and all were reported outside the US (3 from Asia, 2 from South America, and 1 from Canada). The single opportunistic infection in the group receiving the ELNT regimen was a case of *Pneumocystis jiroveci* and cytomegalovirus pneumonia in a patient who received 400 mg ocrelizumab. The 5 opportunistic infections in patients receiving background MMF therapy were tuberculosis (placebo), disseminated herpes zoster, systemic herpes, and cryptococcal meningitis (all 400 mg ocrelizumab), and disseminated herpes/*P jiroveci* (1,000 mg ocrelizumab). MMF doses received by patients experiencing opportunistic infections ranged from 20 to 56 mg/kg/day (before onset of infection). There were 14 deaths during the study; 6 occurred in the placebo-treated group (1 case each of acute myeloid leukemia, acute myocardial infarction, cardiac failure, cardiorespiratory arrest, myocardial infarction, and pulmonary embolism). Three deaths occurred in the 400 mg ocrelizumab–treated group due to cerebral hemorrhage, disseminated intravascular coagulation, and acute renal failure. The 5 deaths in the 1,000 mg ocrelizumab–treated group were caused by pneumonia (n = 3), septic shock, and urosepsis.

Safety was assessed by standard of care regimen. As shown in Table 5, the general incidence of AEs was lower among patients receiving the background ELNT regimen than among those receiving background MMF (72.1% versus 92.4%). The incidence of infusion-related reactions was also lower in those receiving the background ELNT regimen (7.1%, versus 14.3% for those receiving background MMF). Ocrelizumab-treated patients receiving the background ELNT regimen also had a lower incidence of serious AEs than did those receiving background MMF (Table 5). Overall, the proportion of patients with infections was lower in those receiving the background ELNT regimen than in those receiving background MMF (48.6% versus 68.5%). This was also the case for serious infections; rates per 100 patient-years were similar among the treatment groups for patients receiving the background ELNT regimen (17.5 [95% CI 8.3, 36.6], 18.7 [95% CI 9.3, 37.3], and 19.0 [95% CI 9.5, 38.0] for the placebo-treated, 400 mg ocrelizumab–treated, and 1,000 mg ocrelizumab–treated groups, respectively). Patients receiving background MMF who received ocrelizumab had higher serious infection rates per 100 patient-years (34.5 [95% CI 23.5, 50.7] and 28.6 [95% CI 18.6, 43.8] for 400 mg ocrelizumab and 1,000 mg ocrelizumab, respectively) than those who received placebo (19.4 [95% CI 11.5, 32.7]). Most serious infections occurred during the first 12 weeks of treatment for both standard of care therapies (data not shown), and serious infection rates for all treatment groups were considerably lower between weeks 12 and 48.

DISCUSSION

Owing to the early stopping and unblinding of this study and the inherent difficulty with interpreting clinical data collected under these circumstances, efficacy results for the primary outcome focused on a subset of patients who received treatment for a period of at least 32 weeks. In these patients, overall renal response rates were similar with both doses of ocrelizumab plus background standard of care, with an estimated treatment difference of 12.7% versus placebo. The early stopping of the trial limited the assessment of efficacy to changes observed at 48 weeks, and therefore any poten-

tial benefits of ocrelizumab treatment on long-term renal performance could not be determined.

Addition of ocrelizumab to MMF did not appear to provide any further benefit in terms of overall renal response, while addition of ocrelizumab to an ELNT regimen did lead to some improvement in overall renal response. An exploratory ad hoc analysis found that patients with baseline IV glucocorticoid doses ≥1,000 mg generally achieved higher overall renal response rates (and addition of ocrelizumab for this subgroup did not appear to further increase the overall renal response rate). As a smaller proportion of placebo-treated patients receiving a background ELNT regimen received baseline IV glucocorticoid doses ≥1,000 mg compared with placebo-treated patients receiving background MMF (n = 3 [11%] versus n = 24 [51%]), this may provide an explanation for the lower overall renal response rates observed with the ELNT regimen. The placebo-treated patients receiving a background ELNT regimen had unexpectedly low renal response rates compared with previous results from the Euro-Lupus Nephritis Trial (5). Glucocorticoid dosing may explain this difference, as patients in the Euro-Lupus Nephritis Trial (5) received a much higher baseline glucocorticoid dose (3 × 750 mg pulses of IV methylprednisolone) compared with the vast majority of patients receiving a background ELNT regimen in the present study. Although background glucocorticoid dosing could explain differences in ocrelizumab efficacy in combination with the 2 background regimens, the study was not designed to compare efficacy between the 2 regimens, and no conclusions about this could be drawn from these observations.

Similar to results seen in the rituximab LUNAR trial, ocrelizumab treatment led to increases in complement levels (C3, C4) and a reduction in anti-dsDNA levels. Furthermore, in exploratory analyses, the subgroup of patients with normal complement levels did not show an increase in overall renal response rates with ocrelizumab. The observed difference in overall renal response rates between the ocrelizumab- and placebo-treated groups was restricted to the subgroup of patients with lower/abnormal serologic parameter levels at baseline.

With regard to safety, the frequency of infusion reactions was typically highest with the first infusion and then reduced with successive infusions—a consistent finding across several diseases treated with anti-CD20 therapies. This difference is presumably due to a larger B cell number and subsequent cytokine release with the first infusion.

An increase in the rates of serious AEs and serious infections was observed with 400 mg ocrelizumab, but not with the higher dose. The reason for the apparent difference in serious infection rates between the ocrelizumab doses is unclear. In general, serious infection rates were lower among patients receiving background CYC/AZA. Indeed, the addition of ocrelizumab (either dose) to background CYC/AZA did not lead to an increase in the rate of serious infections. In contrast, patients receiving background MMF who received ocrelizumab showed an increase in serious infection rates compared with those who received placebo, with little difference between the doses.

One potential explanation for the apparently higher rate of infections in the group who received background MMF is the dose of baseline IV glucocorticoids; a greater proportion of patients who received background MMF than patients who received a background ELNT regimen received a baseline IV glucocorticoid dose ≥1,000 mg. The combination of a different B cell–targeted treatment, atacicept, with background MMF was associated with rapid onset of hypogammaglobulinemia and severe infection in LN patients (27). A similar interaction between ocrelizumab and MMF in LN patients with proteinuria may provide an explanation for the increased rate of serious infections in the current study. Other differences in ocrelizumab safety were also observed between the 2 background standard of care regimens. There was a trend toward a higher rate of AEs with background MMF compared with the background ELNT regimen. In particular, patients who received MMF tended to report diarrhea more frequently than did those receiving the background ELNT regimen, an observation that was not unexpected (28).

The timing of serious infections is also of interest. The majority of serious infections occurred during the first 12 weeks of the study, irrespective of background standard of care. One explanation for this observation is the higher levels of concomitant glucocorticoid medication and higher overall disease activity in patients during the early period of the study. Overall, patients who had serious infections during the 48-week treatment period received a somewhat higher level of equivalent prednisone doses compared with patients who did not have serious infections, regardless of treatment group (mean ± SD 19 ± 10 mg/day versus 15 ± 8 mg/day).

Analysis of the rates of infections and serious infections indicated a clear difference between patients who were recruited in Asia and those who were not. The reasons for this difference are currently not known but are unlikely to involve differences in baseline immuno-

globulin levels, concomitant mean prednisone doses, or weight-adjusted MMF doses, which were comparable between Asian and non-Asian patients in this study (data not shown). The differences could instead have been a result of differences in the use of other concomitant medications or other patient characteristics, such as longer LN duration or higher proteinuria among Asian patients. Another possible factor could be a higher prevalence of, or susceptibility to, certain infectious diseases in Asia. The lower average body weight of Asian patients could also have led to higher by-weight ocrelizumab dosing among these patients. The dose per weight was not different between Asian and non-Asian patients receiving 400 mg ocrelizumab (mean dose per 60 kg body weight: 1.4 gm in Asians versus 1.4 gm in non-Asians) but was higher among Asian patients receiving 1,000 mg ocrelizumab (3.8 gm versus 3.2 gm). The higher rates of serious infections seen in Asian patients who received ocrelizumab are consistent with results from the ocrelizumab RA clinical trials (24,25). Higher infection rates among Asian patients were also observed in the Aspreva Lupus Management Study trial (9).

Although the incidence of serious opportunistic infections was low, an apparent imbalance was observed between the 400 mg ocrelizumab– and placebo-treated groups (3.2% versus 0.8%, respectively) that was not seen with 1,000 mg ocrelizumab (0.8%). This increased frequency of serious opportunistic infections was the principal reason for study termination.

In conclusion, patients with severe LN who received ocrelizumab in combination with standard of care therapy had a higher incidence of infections (serious or opportunistic) compared with those receiving placebo plus standard of care. This study was terminated early by the sponsor following a reassessment of the benefit/risk ratio of anti-CD20 therapy in LN. Therefore, definitive conclusions cannot be drawn regarding the beneficial effect of adding ocrelizumab to MMF or ELNT CYC background therapy. Ocrelizumab continues to be investigated as a potential treatment for multiple sclerosis (29).

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All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Mysler had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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ADDITIONAL DISCLOSURES

Authors Drappa and Close are employees of MedImmune.

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